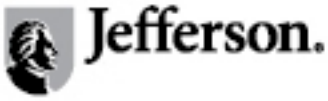

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Efficacy and tolerability of adjunctive brivaracetam in patients with prior antiepileptic drug exposure: A post-hoc study.

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Efficacy and tolerability of adjunctive brivaracetam in patients with prior antiepileptic drug exposure: A post-hoc study

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ABSTRACT

Brivaracetam (BRV), a selective, high-affinity ligand for synaptic vesicle protein 2A, is a new antiepileptic drug (AED) for adjunctive treatment of focal (partial-onset) seizures in adults with epilepsy. This post-hoc analysis was conducted to explore the efficacy of adjunctive BRV in patients with prior levetiracetam (LEV) exposure and whether changes in efficacy were related to the similar mechanism of action of these two drugs. Data were pooled from three Phase III studies (NCT00490035; NCT00464269; NCT01261325) of adults with focal seizures taking 1–2 AEDs who received placebo or BRV 50–200 mg/day without titration over a 12-week treatment period. Patients taking concomitant LEV at enrollment were excluded from this analysis. Patients were categorized by their status of prior exposure to LEV, carbamazepine (CBZ), topiramate (TPM), or lamotrigine (LTG), to investigate any consistent trend towards reduced response in AED-exposed subgroups compared to AED-naïve subgroups, regardless of the mechanism of action. Study completion rates, percent reduction from baseline in focal seizure frequency over placebo, ≥50% responder rates, and tolerability were evaluated for each subgroup. A total of 1160 patients were investigated. Study completion rates were similar in the AED-exposed subgroups and AED-naïve subgroups. In subgroups with (531 patients) or without (629 patients) prior LEV exposure, ≥50% responder rates for each dose of BRV compared with placebo were generally higher among the LEV-naïve subgroups than the previously LEV-exposed subgroups. LEV-exposed subgroups receiving BRV doses ≥50 mg/day showed greater ≥50% responder rates than those receiving placebo. Similar results were observed for CBZ, TPM, and LTG. Previous treatment failure with commonly prescribed AEDs (LEV, CBZ, TPM, or LTG) is associated with a reduced response to BRV irrespective of the mechanism of action. Hence, this post-hoc analysis indicates that previous treatment failure with LEV does not preclude the use of BRV in patients with epilepsy.

1. Introduction

Brivaracetam (BRV) is a new antiepileptic drug (AED) derived from a targeted drug discovery program (Klitgaard et al., 2016). BRV is a selective, high-affinity ligand for synaptic vesicle protein 2A (SV2A) (Gillard et al., 2011). Its binding affinity with SV2A is higher than that of levetiracetam (LEV), another SV2A ligand (Gillard et al., 2011). The tolerability and efficacy of adjunctive BRV in patients with drug-resistant focal (partial-onset) seizures with or without secondary generalization have been investigated and demonstrated in three pivotal Phase III studies (Biton et al., 2014; Klein et al., 2015a; Rheims and Ryvlin, 2014). One recent meta-analysis (Ma et al., 2015) identified five randomized, controlled trials of BRV in the treatment of drug-resistant focal epilepsies and included a total of 1639 patients. This meta-analysis demonstrated a statistically significant improvement in seizure control compared with placebo, and favorable tolerability of therapeutic doses of BRV (50–200 mg/day) as an adjunctive treatment for drug-resistant focal epilepsy.

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Approximately one-third of individuals with epilepsy have inadequate seizure control despite the use of appropriate AEDs (Kwan and Brodie, 2000b). In addition, treatment in patients with epilepsy is often complicated by the unpredictability of the efficacy of any given AED. This uncertainty of response, particularly in patients with drug-resistant seizures, may obfuscate the use of any newly developed AED (Kwan et al., 2010). This is particularly important if the newly developed AED has similarities to an already existing AED. For example, it is helpful to know whether failure of a currently available AED, such as LEV, precludes the prescription of a newly developed AED (i.e. BRV) that also targets one of the same molecular sites of action. It is noteworthy that BRV differs significantly from LEV by its selective, high affinity, and differential interaction with SV2A, as well as a higher lipophilicity, correlating with a more rapid brain penetration in preclinical studies (Klitgaard et al., 2016). BRV also differs from LEV by neither inhibiting the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Margineanu and Klitgaard, 2002; Rigo et al., 2004) nor the high voltage-activated calcium channels at therapeutically relevant concentrations (Klitgaard et al., 2016; Niespodziany et al., 2015; Pisani et al., 2004). In a post-hoc analysis of study N01358, efficacy with adjunctive BRV was demonstrated in subgroups with prior LEV exposure and also in LEV-naïve patients, but the response appeared to be greater in the LEV-naïve population (Klein et al., 2015a). The aim of the current post-hoc analysis was to explore the efficacy of adjunctive BRV in patients with or without prior LEV exposure in a larger patient population pooled from three Phase III studies, and to determine whether any observed trend towards reduced efficacy in LEV-exposed patients compared with LEV-naïve patients was related to mechanism of action. Some other commonly prescribed AEDs [carbamazepine (CBZ), lamotrigine (LTG), and topiramate (TPM)] were also investigated to see whether prior exposure to these drugs was related to BRV efficacy. Tolerability data were evaluated for each subgroup. These data may be helpful in the decision-making process when considering the use of BRV for patients who have previously failed other AEDs.

2. Methods

This is a post-hoc analysis of data pooled from three Phase III studies (N01252, NCT00490035; N01253, NCT00464269; N01358, NCT01261325) (Biton et al., 2014; Klein et al., 2015a; Rheims and Ryvlin, 2014). All patients included in this analysis were randomized to BRV 50, 100, and 200 mg per day or placebo. Patients who were on concomitant LEV at the time of enrollment were excluded from this analysis. Patients were categorized by their status of prior exposure to LEV, CBZ, TPM, or LTG. We defined AED-naïve as "never having been exposed to that particular AED" and AED-exposed as "having been exposed to that particular AED" (during the past 5 years for studies N01252 and N01253, and during the patient's lifetime before study entry for study N01358). For AED-exposed patients, that specific AED had to have been discontinued at least 90 days prior to enrollment in the Phase III study. Demographic and baseline epilepsy characteristics, and the number (%) of patients who completed the study, were summarized for each subgroup.

The efficacy population comprised all randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry. Percent reduction from baseline in focal seizure frequency over placebo, and ≥50% responder rates, were evaluated for each subgroup of patients. A further subgroup analysis was conducted for ≥50% responder rate based on the number of prior AEDs (≤2, 3–5, and ≥6). This subgroup analysis was conducted on a modified efficacy population that included patients taking concomitant LEV. In this analysis, a prior AED was defined as any AED that was taken previously and/or concomitantly at study entry.

Treatment group comparisons (BRV ≥50 mg/day vs. placebo) for ≥50% responder rates were based on a logistic regression model with ≥50% responder rate as the outcome, and with effects for treatment, study, and log-transformed baseline focal seizure frequency as a continuous covariate. The logistic regression model was used to examine the relationship between the ≥50% responder rate and a set of predictor variables. The model used a logit transformation of the outcome, which is the log of the odds or the ratio of the probability of the outcome (yes for ≥50% response) to the probability of no outcome (no for ≥50% response). All statistical analyses were exploratory.

Details of the study population, efficacy assessments, safety and tolerability assessments, and ethical issues are explained in the previous Phase III studies (Biton et al., 2014; Klein et al., 2015a; Rheims and Ryvlin, 2014).

3. Results

A total of 1160 patients were included in this analysis. Overall, 531 patients had previously been exposed to LEV and 629 were LEV-naïve. Demographic and baseline epilepsy characteristics are shown in Table 1. Demographic characteristics were similar between the AED-exposed and AED-naïve subgroups. However, the proportion of patients who had previously failed at least 5 AEDs was higher among previously LEV-, CBZ-, TPM-, and LTG-exposed subgroups (61–69%) than among subgroups who had never taken those particular AEDs (13–17%).

Table 1
Demographic and baseline epilepsy characteristics, by prior exposure to levetiracetam, carbamazepine, topiramate, or lamotrigine (efficacy population).

	Levetiracetam		Carbamazepine		Topiramate		Lamotrigine	
	Exposed (*n* = 578)	Naïve (*n* = 743)	Exposed (*n* = 424)	Naïve (*n* = 339)	Exposed (*n* = 428)	Naïve (*n* = 696)	Exposed (*n* = 349)	Naïve (*n* = 639)
Age, mean (SD), years	39.8 (13.3)	36.9 (12.6)	39.6 (13.5)	37.4 (14.2)	38.5 (12.8)	38.3 (13.4)	39.7 (13.2)	38.0 (13.1)
Female, *n* (%)	318 (55.0)	341 (45.9)	229 (54.0)	165 (48.7)	232 (54.2)	306 (44.0)	188 (53.9)	282 (44.1)
No. of prior AEDs, *n* (%)								
0–1	29 (5.0)	304 (40.9)	24 (5.7)	136 (40.1)	11 (2.6)	280 (40.2)	5 (1.4)	263 (41.2)
2–4	176 (30.4)	343 (46.2)	140 (33.0)	145 (42.8)	123 (28.7)	310 (44.5)	107 (30.7)	280 (43.8)
≥5	373 (64.5)	96 (12.9)	260 (61.3)	58 (17.1)	294 (68.7)	106 (15.2)	237 (67.9)	96 (15.0)
Baseline focal seizure frequency/28 days, median (Q1, Q3)	11.0 (6.4, 26.8)	7.9[a] (5.0, 15.9)	9.6 (5.8, 24.2)	8.3 (5.5, 19.2)	9.7 (5.8, 24.5)	8.5[b] (5.3, 18.8)	11.3 (6.1, 25.8)	8.0[c] (5.1, 16.9)

The efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were excluded.
[a] n = 742, [b] n = 695, [c] n = 638; patients without baseline seizure frequency were excluded.
AED, antiepileptic drug; Q1, first quartile; Q3, third quartile; SD, standard deviation.

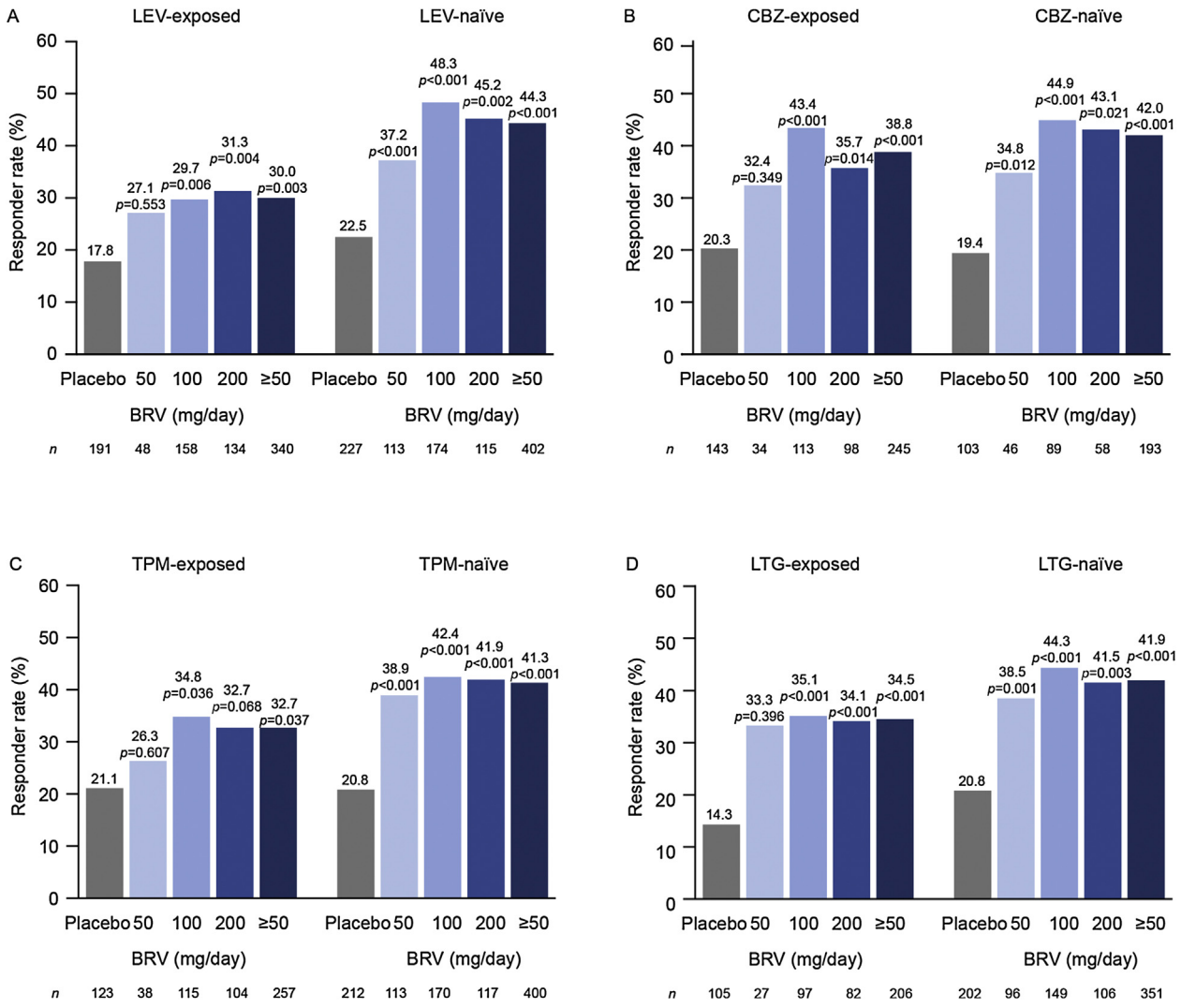

Fig. 1. ≥50% responder rates in patients treated with brivaracetam, with or without prior levetiracetam (A), carbamazepine (B), topiramate (C) or lamotrigine (D) exposure (efficacy population).
p-values (BRV vs. placebo) are derived from a logistic regression model with effects for treatment, study, and log-transformed baseline focal seizure frequency as a continuous covariate. All *p*-values are exploratory. The efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were excluded.
BRV, brivaracetam; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate.

Numbers of patients enrolled, study completion (retention) rates, and percent reduction from baseline in focal seizure frequency over placebo for each subgroup of patients are shown in Tables 2–5, and ≥50% responder rates for each subgroup of patients are shown in Fig. 1.

Retention rates, which are predominantly a reflection of tolerability, were similar in the AED-exposed and AED-naïve subgroups. The 12-week retention rates during the study period were >84% in all subgroups (all doses and all drugs) (Tables 2–5).

Percent reduction from baseline in focal seizure frequency over placebo was numerically greater in BRV-treated, LEV-naïve subgroups than in BRV-treated, LEV-exposed subgroups (Table 2). A similar pattern was seen for subgroups with and without prior exposure to CBZ, TPM, and LTG (Tables 3–5).

The ≥50% responder rates for BRV compared with placebo were higher among the LEV-naïve subgroups than the LEV-exposed subgroups (Fig. 1A). However, LEV-exposed subgroups receiving BRV doses ≥50 mg/day showed higher ≥50% responder rates than corresponding placebo subgroups. Similar results were observed in subgroups with or without prior CBZ, TPM, and LTG exposure, although the differences between the corresponding AED-exposed and AED-naïve subgroups for BRV versus placebo were less marked for CBZ and LTG (Fig. 1B–D).

Responder rates for subgroups of patients with ≤2, 3–5, and ≥6 prior AED exposures are shown in Table 6. When the number of prior AEDs was 3–5, the LEV-naïve subgroup showed a greater response with BRV, compared with placebo, than the LEV-exposed subgroup. A similar trend was observed with other AEDs (i.e. CBZ, TPM, and LTG). In subgroups with ≤2 prior AEDs, the number of patients was too small for statistical analysis. No clear pattern was seen in subgroups with ≥6 prior AED exposures.

4. Discussion

BRV is a new AED that has demonstrated efficacy as an adjunctive treatment for adults with focal epilepsies and has been shown to be well tolerated (Biton et al., 2014; Klein et al., 2015a; Kwan et al., 2014; Rheims and Ryvlin, 2014). A previous post-hoc analysis indicated that adjunctive BRV was effective both in subgroups of patients with prior exposure to LEV and in those who were

Table 2
Numbers of patients enrolled, study completion rates (over 12 weeks), and percent reduction from baseline in focal seizure frequency over placebo in patients treated with brivaracetam (BRV), with or without prior levetiracetam (LEV) exposure (efficacy population).

	Placebo	BRV 50 mg/day	BRV 100 mg/day	BRV 200 mg/day	BRV ≥50 mg/day	
LEV- exposed	Number of patients	191	48	158	134	340
	Number of patients who completed the study (%)	184 (96.3)	43 (89.6)	141 (89.2)	119 (88.8)	303 (89.1)
	Percent reduction from baseline in focal seizure frequency over placebo	–	5.1	17.3	20.3	12.8
LEV- naïve	Number of patients	227	113	174	115	402
	Number of patients who completed the study (%)	212 (93.4)	104 (92.0)	158 (90.8)	106 (92.2)	368 (91.5)
	Percent reduction from baseline in focal seizure frequency over placebo	–	26.1	30.0	27.3	28.7

The efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were excluded.

Table 3
Numbers of patients enrolled, study completion rates (over 12 weeks), and percent reduction from baseline in focal seizure frequency over placebo in patients treated with brivaracetam (BRV), with or without prior carbamazepine (CBZ) exposure (efficacy population).

	Placebo	BRV 50 mg/day	BRV 100 mg/day	BRV 200 mg/day	BRV ≥50 mg/day	
CBZ- exposed	Number of patients	143	34	113	98	245
	Number of patients who completed the study (%)	137 (95.8)	31 (91.2)	100 (88.5)	88 (89.8)	219 (89.4)
	Percent reduction from baseline in focal seizure frequency over placebo	–	5.4	23.1	19.2	15.0
CBZ- naïve	Number of patients	103	46	89	58	193
	Number of patients who completed the study (%)	96 (93.2)	39 (84.8)	81 (91.0)	51 (87.9)	171 (88.6)
	Percent reduction from baseline in focal seizure frequency over placebo	–	23.3	30.3	17.7	26.4

The efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were excluded.

Table 4
Numbers of patients enrolled, study completion rates (over 12 weeks), and percent reduction from baseline in focal seizure frequency over placebo in patients treated with brivaracetam (BRV), with or without prior topiramate (TPM) exposure (efficacy population).

	Placebo	BRV 50 mg/day	BRV 100 mg/day	BRV 200 mg/day	BRV ≥50 mg/day	
TPM- exposed	Number of patients	123	38	115	104	257
	Number of patients who completed the study (%)	120 (97.6)	35 (92.1)	99 (86.1)	90 (86.5)	224 (87.2)
	Percent reduction from baseline in focal seizure frequency over placebo	–	13.1	17.9	18.2	13.1
TPM- naïve	Number of patients	212	113	170	117	400
	Number of patients who completed the study (%)	197 (92.9)	104 (92.0)	158 (92.9)	108 (92.3)	370 (92.5)
	Percent reduction from baseline in focal seizure frequency over placebo	–	24.4	29.6	31.3	28.6

The efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were excluded.

Table 5
Numbers of patients enrolled, study completion rates (over 12 weeks), and percent reduction from baseline in focal seizure frequency over placebo in patients treated with brivaracetam (BRV), with or without prior lamotrigine (LTG) exposure (efficacy population).

	Placebo	BRV 50 mg/day	BRV 100 mg/day	BRV 200 mg/day	BRV ≥50 mg/day	
LTG- exposed	Number of patients	105	27	97	82	206
	Number of patients who completed the study (%)	102 (97.1)	24 (88.9)	83 (85.6)	74 (90.2)	181 (87.9)
	Percent reduction from baseline in focal seizure frequency over placebo	–	1.8	22.5	24.0	13.1
LTG- naïve	Number of patients	202	96	149	106	351
	Number of patients who completed the study (%)	190 (94.1)	90 (93.8)	139 (93.3)	96 (90.6)	325 (92.6)
	Percent reduction from baseline in focal seizure frequency over placebo	–	28.0	30.6	28.5	29.1

The efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were excluded.

LEV-naïve, although the effect appeared to be greater in the LEV-naïve population (Klein et al., 2015a). In the current post-hoc analysis, we investigated whether prior exposure to – and failure of – specific, commonly used AEDs (i.e. LEV, CBZ, TPM, or LTG) is a marker for lack of response to BRV in patients with drug-resistant focal epilepsy, a hypothesis that was not confirmed by the results.

AED treatment in patients with epilepsy is often complicated by many factors, including the unpredictability of efficacy (Kwan et al., 2010). It has been observed that, if the first appropriately chosen AED is not efficacious in controlling seizures, the outcome with respect to seizure control is less favorable with the next prescribed AED (Kwan and Brodie, 2000a). In a cohort of 478 patients who

Table 6
≥50% responder rates, by prior AED exposure and number of prior AEDs (modified efficacy population).

	Number of prior AEDs					
	≤2		3–5		≥6	
	Placebo	BRV ≥50 mg/day	Placebo	BRV ≥50 mg/day	Placebo	BRV ≥50 mg/day
LEV-exposed	Number of patients	15	14	61	105	115	221
	≥50% responder rate, *n* (%)	3 (20.0)	7 (50.0)	15 (24.6)	37 (35.2)	16 (13.9)	58 (26.2)
			$p = 0.128$		$p = 0.224$		$p = 0.010$
LEV-naïve	Number of patients	94	180	106	178	27	44
	≥50% responder rate, *n* (%)	23 (24.5)	84 (46.7)	23 (21.7)	75 (42.1)	5 (18.5)	19 (43.2)
			$p < 0.001$		$p < 0.001$		$p = 0.088$
CBZ-exposed	Number of patients	12	20	56	94	82	153
	≥50% responder rate, *n* (%)	4 (33.3)	13 (65.0)	16 (28.6)	39 (41.5)	10 (12.2)	46 (30.1)
			$p = 0.034$		$p = 0.099$		$p = 0.007$
CBZ-naïve	Number of patients	54	89	52	90	18	40
	≥50% responder rate, *n* (%)	14 (25.9)	41 (46.1)	8 (15.4)	32 (35.6)	3 (16.7)	11 (27.5)
			$p = 0.030$		$p = 0.011$		$p = 0.291$
TPM-exposed	Number of patients	5	11	44	82	82	182
	≥50% responder rate, *n* (%)	4 (80.0)	4 (36.4)	13 (29.5)	31 (37.8)	12 (14.6)	51 (28.0)
			$p = 0.150$		$p = 0.652$		$p = 0.025$
TPM-naïve	Number of patients	92	180	108	197	40	62
	≥50% responder rate, *n* (%)	19 (20.7)	79 (43.9)	23 (21.3)	74 (37.6)	6 (15.0)	18 (29.0)
			$p < 0.001$		$p = 0.003$		$p = 0.058$
LTG-exposed	Number of patients	10	12	33	53	71	157
	≥50% responder rate, *n* (%)	0 (0)	6 (50.0)	5 (15.2)	20 (37.7)	13 (18.3)	46 (29.3)
					$p = 0.054$		$p = 0.109$
LTG-naïve	Number of patients	84	160	109	162	29	56
	≥50% responder rate, *n* (%)	20 (23.8)	73 (45.6)	22 (20.2)	61 (37.7)	3 (10.3)	17 (30.4)
			$p = 0.001$		$p = 0.003$		$p = 0.045$

All *p*-values are exploratory. The modified efficacy population comprised randomized patients who received at least one dose of study drug and had at least one post-baseline seizure diary entry; patients taking concomitant LEV were included.
AED, antiepileptic drug; BRV, brivaracetam; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; TPM, topiramate.

received newly administered AED treatments in a single epilepsy clinic (Schiller and Najjar, 2008), the response to newly administered AEDs was highly dependent on the past treatment history. Seizure freedom rates decreased from 61.8% for the first AED to 41.7%, 16.6%, and 0% after 1, 2–5, and 6–7 prior AED failures, respectively. In the current study, we observed that BRV, compared with placebo, is more efficacious in AED-naïve subgroups than in those who have previously been exposed to any of the particular AEDs tested (i.e. LEV, CBZ, TPM, and LTG). In other words, exposure to prior AEDs can predict a reduced response to BRV. It is likely that mechanism of action does not play a major role in this phenomenon, as we observed similar trends with prior exposure to AEDs with different mechanisms of action. We also did not see a consistent pattern of response in subgroups of patients who had previously been exposed to ≥6 AEDs. Because patients with ≥6 prior AED failures are highly unlikely to respond to the next AED, this may be a sufficient reason to exclude this subgroup from the design of future AED trials.

There are various factors that may contribute to the reduced efficacy observed in different patient populations. Genetic variations may explain some of the inter-individual variability in response to AEDs among patients (Franco and Perucca, 2015; Shaheen et al., 2014). The number of previously tried and failed AEDs, which is indicative of drug resistance and severity of epilepsy, may also explain reduced drug responses observed among patients with refractory epilepsy (Klein et al., 2015b; Schiller and Najjar, 2008; Voll et al., 2015). Another plausible mechanism of drug resistance is the overexpression of multidrug efflux transporters, such as P-glycoprotein (P-gp), which would result in lower interstitial levels of AEDs surrounding the epileptogenic tissue (Loscher, 2005; Schmidt and Loscher, 2005; Sisodiya et al., 2002). Animal and human studies support the multidrug transporter hypothesis of multidrug-resistant epilepsy (Asadi-Pooya et al., 2013; Lazarowski and Czornyj, 2011).

Despite the observed reduced efficacy of BRV in AED-exposed subgroups compared to AED-naïve subgroups, BRV was more efficacious when compared with placebo in the AED-exposed subgroups. This observation was consistent for all the investigated prior AEDs. Therefore, BRV was efficacious for the treatment of focal epilepsies even in patients who had been previously exposed to and failed other commonly prescribed AEDs. This is an important finding and offers promise for patients with multidrug-resistant epileptic seizures.

With respect to BRV tolerability, we observed that retention rates were reasonably high (84.8–93.8%) in all dose groups. In several previous studies, including the original studies for the current analysis, BRV has demonstrated a good safety and tolerability profile (Biton et al., 2014; Klein et al., 2015a; Rheims and Ryvlin, 2014). In a small, open-label, prospective, exploratory study of 29 patients with epilepsy switching from LEV to BRV (Yates et al., 2015), non-psychotic behavioral adverse events were evaluated. At the end of the treatment period, 93.1% of patients that switched to BRV had clinically meaningful reductions in behavioral adverse events. Mean change from baseline to Week 12 in Patient-Weighted Quality of Life in Epilepsy Inventory-Form-31 (QOLIE-31-P) total score was 12.1, indicating improved health-related quality of life. These data suggest that BRV may have a better profile with respect to behavioral adverse events compared with LEV (Yates et al., 2015).

As this was a post-hoc study, the results of our analysis should be viewed as exploratory and require confirmation by prospective studies. Furthermore, all *p*-values in this study should be considered in the context of an exploratory analysis. In addition, the numbers of patients in some of the subgroups were too small for valid statistical analysis.

In conclusion, while prior exposure to commonly prescribed AEDs (LEV, CBZ, TPM, and LTG) is associated with a reduced response to BRV, this effect is seen irrespective of the mechanism of action. This is consistent with the previous studies cited above, showing that the likelihood of response to any AED decreases as the number of prior AEDs increases. This post-hoc analysis therefore indicates that previous treatment failure with LEV does not preclude the use of BRV.

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Disclosures

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